Remarks

Applicants thank Examiners Gibbs and Wang for the helpful interview held March 28, 2005. This reply includes the substance of that interview.

Amendments to the Claims

Claim 22 is amended to recite measuring a first and a second expression level of the recited mRNA and protein in samples of a "biological subject comprising" precancerous or cancer cells and that the treatment regimen "effectively reduced the number of precancerous or cancer cells in the biological subject." Section E on page 56, line 10, to page 57, line 2 of the specification ("Methods for Monitoring Efficacy of Cancer Treatment"), supports these amendments.

Independent claim 33 is amended to recite a method of diagnosing breast cancer. Diagnosis of breast cancer is disclosed, for example, in the paragraph spanning pages 11 and 12 of the specification.

New dependent claims 44-48 recite that the mammal is a human; these claims are supported on page 5, lines 16-19: "The present invention relates to isolation, characterization, overexpression and implication of genes, including amplified genes, in cancers, methods and compositions for the diagnosis, prevention, and treatment of tumors and cancers, for example, ovarian cancer, in mammals, for example, humans."

New dependent claims 49-50 recite prostate, breast, and lung tissue respectively; these recitations previously were present in claim 2.

New claim 52 is directed to a method for diagnosing a cancer by determining a hepsin gene copy number in a biological subject from a mammal. New dependent claim 53 recites that

the mammal is a human, and new dependent claims 54-57 recite that the biological subject is ovarian, prostate, breast, and lung tissue. These claims are supported on page 6, line 29, to page 7, line 4:

> In one aspect, the present invention provides a method for diagnosing a cancer, for example, an ovarian cancer, a prostate cancer, a lung cancer, or a breast cancer, etc., in a mammal, which comprises, for example, obtaining a biological test sample from a region in the tissue that is suspected to be precancerous or cancerous; and measuring in the biological subject the number of hepsin gene copies thereby determining whether the hepsin gene is amplified in the biological test subject, wherein amplification of the hepsin gene indicates a cancer in the tissue.

New claim 58 parallels claims 3, 11, 14, 24, and 35.

New independent claims 59 and 62 recite determining a first and a second indirect measure of hepsin gene copy number. These claims are supported on pages 41-43 and in Example 1 of the specification, which describe a variety of techniques for indirectly measuring copy gene number.

Other amendments to the claims either clarify the recited subject matter or result from amendments to the independent claims. None of the amendments adds new matter.

The Rejection of Claims 1-3, 9-12, 14, 22-24, and 33-35 Under 35 U.S.C. § 112, first paragraph

Claims 1-3, 9-12, 14, 22-24, and 33-35 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled. The enablement rejection is based on an asserted requirement that "specific threshold embodiments must be met and achieved to accomplish the instant methods." Applicants respectfully request withdrawal of the rejection.

At the interview held March 28, Applicants' representatives explained that the "detectable" limit is based on the "instrument detection limit" inherent in techniques used to detect and measure gene copy number. For example, the specification teaches that a Taqman 7700 instrument cannot easily distinguish one copy from a two-fold increase of gene copies. Therefore, for example, with this instrument a threshold of 2.5 fold was considered to be hepsin gene amplification. See page 65, lines 9-13 of the specification. Applicants also explain, however, that an increase in hepsin gene copy number less than 2.5 fold can still be considered as an amplification of the gene. *Id.*

The threshold will be different for each technique or instrument used to detect and measure gene copy number (indeed, it may differ for the same technique employing, for example, different instrumentation). This is why the independent claims recite that the "detectable" rather than any particular threshold number. This does not mean, however, that determination of a detectable level of hepsin gene amplification would require undue experimentation.

Methods of detecting and measuring gene amplification are well known in the art. As the specification teaches, these techniques include Southern blotting, *in situ* hybridization, comparative genomic hybridization (CGH), amplification-based assays (*e.g.*, a PCR-based TaqMan assay), and DNA microarray-based CGH (pages 41-43; Example 1). Determination of

what instrument detection limit represents gene amplification for any of these techniques would be merely routine. Therefore, skilled artisan would be able to practice the claimed methods without undue experimentation.

After the discussion during the March 28 interview, as indicated on the Interview Summary, the Examiner agreed to withdraw the rejection under 35 U.S.C. § 112, first paragraph. Applicants thank the Examiner for the withdrawal.

The Rejection of Claims 1-3 and 39 Under 35 U.S.C. § 102(b)

Claims 1-3 and 39 stand rejected under 35 U.S.C. § 102(b) as anticipated by Tanimoto *et al.*, *Cancer Res. 57*, 2884-87, 1997 ("Tanimoto"). Applicants respectfully traverse the rejection.

A reference cited under 35 U.S.C. § 102 must expressly or inherently describe each element set forth in the rejected claim. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Independent claim 1 recites a method comprising a step of determining an indirect measure hepsin gene copy number in a biological subject from a region of a mammal that is suspected to be precancerous or cancerous. Tanimoto neither explicitly nor inherently teaches methods of indirectly determining hepsin gene copy number.

Tanimoto teaches use of quantitative PCR "to evaluate the mRNA expression of hepsin in ovarian tumors." Tanimoto at page 2885, last paragraph, emphasis added. Tanimoto does not explicitly teach using quantitative PCR to measure the number of hepsin gene copies in the tumors.

Nor does Tanimoto's method inherently provide an indirect measure of hepsin gene copy number. An inherent feature must necessarily be present in the prior art disclosure:

> Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. [Citations omitted.] If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.

Hansgirg v. Kemmer, 102 F.2d 212, 214, 40 U.S.P.Q. 665, 667 (C.C.P.A. 1939). If the disclosure itself is not sufficient to show the inherent element, extrinsic evidence must be used to "make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *In re Robertson*, 169 F.3d 743, 745, 49 U.S.P.Q.2d 1949, 1950-51 (Fed. Cir. 1999). *See also* M.P.E.P. § 2112 (IV) ("EXAMINER MUST PROVIDE RATIONALE OR EVIDENCE TENDING TO SHOW INHERENCY").

In this case, extrinsic evidence shows that a measurement of mRNA expression does not necessarily provide an indirect measure of hepsin gene copy number. Table 2 on page 39 of the specification provides several examples of ovarian tumor samples in which the indirect measure of hepsin gene copy number is the same, whereas the levels of hepsin mRNA expression in the same ovarian tumor samples is quite different. The Table below contains excerpts of the data from Table 2.

IDENTIFIER	HEPSIN DNA COPY NUMBER	RELATIVE HEPSIN MRNA LEVEL
CHTN 277	0.61	156
CHTN 279	0.61	64
CHTN 577	3.5	399
CHTN 564	3.5	523
CHTN 531	3.3	104
CHTN 380	3.3	25
CHTN 285	0.78	190
CHTN 290	0.78	357

These data in the specification show that hepsin mRNA expression does not necessarily correlate with hepsin gene copy number and demonstrate that Tanimoto's measurement of hepsin mRNA expression in an ovarian tumor does not necessarily provide an indirect measure of hepsin gene copy number in the tumor. Thus, Tanimoto does not inherently disclose determining indirect measures of hepsin gene copy number, as recited in claim 1.

Tanimoto neither explicitly nor inherently teaches each element recited in claim 1 and therefore does not anticipate independent claim 1 or dependent claims 2, 3, or 39.

Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 33-35 Under 35 U.S.C. § 102(b)

Claims 33-35 stand rejected under 35 U.S.C. § 102(b) as anticipated by Zacharski *et al.*, *Thromb. Haemost. 79*, 876-77, 1998 ("Zacharski"). Applicants respectfully traverse the rejection.

The Office Action cites Zacharski as teaching overexpression of hepsin protein in tumors. Paragraph bridging pages 5 and 6 of the Office Action. Applicants have amended claim 33 to recite a method of diagnosing breast cancer. Zacharski teaches nothing about hepsin expression in breast cancer. Zacharski therefore does not anticipate amended independent claim 33 or dependent claims 34 and 35.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,
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